A SERIES OF FOUR CASE HISTORIES

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BY

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Introduction

These cases have been drawn from my clinical attachments in the 4th and 5th years of my medical studies. I have used the case-reports to illustrate points of interest which are discussed immediately after each report.

The first report was taken from my attachment at Bangour General Hospital, the second and third from the Royal Infirmary of Edinburgh and the last report is from the Royal Hospital for Sick Children in Edinburgh.

Permission

Permission was gained to report each case from the consultant concerned.

CASE REPORT 1

Mr V.K. Age 59

Mr V.K. came to Scotland from Yugoslavia after World War II. He worked as a manager for I.B.M. until ill health forced his early retirement in 1984. He lived in Linlithgow and was happily married, with no children. His father died aged 43 and his mother aged 56, both from myocardial infarction. His 53 year old sister has arthritis and liver cirrhosis. He smoked 40 cigarettes daily until the age of 55. He drank alcohol only occasionally.

Mr V.K. was admitted to the medical wards at Bangour General Hospital during my attachment there as a student in June 1988. Previously he had cardiac catheterisation carried out on him at Edinburgh Royal Infirmary and was too ill to go home.

On the ward he complained of severe shortness of breath on exertion, limiting his walking distance to a few yards. He had no symptoms of angina pectoris. He had a cough productive of yellow sputum. He had no haemoptysis or pleuritic chest pain.

His past medical history was revealing. He had jaundice as a child. He suffered sciatica aged 40. At the age of 48 he had a large anteroseptal myocardial infarction, from which he recovered except for a few anginal symptoms. His cholesterol and triglyceride levels were normal. 7 years later he had increasing shortness of breath and two incidents of tight chest pain. No acute changes were found to confirm a further

myocardial infarction, however JVP was markedly raised, gallop rhythm and pulmonary and peripheral oedema were present. A year later at the age of 55 Mr V.K. felt continually weak and unable to work. A Chest X-Ray revealed gross cardiac enlargement. A ventriculogram showed a dilated and globular left ventricle with apical paradox suggesting the presence of a ventricular aneurysm. Left ventricular ejection fraction was 15% at a heart rate of 90/minute. Mr V.K. was able to manage reasonable at home until February 1988 when he was admitted to Murrayfield Hospital, Edinburgh with jaundice. Liver function tests showed mild hepatic dysfunction, bilirubin 37 μmol/l. Hepatic enlargement was found on ultrasound scan. It was considered that this was secondary to cardiac failure since liver biopsy failed to show any definite pathology. In April 1988 Mr V.K. was admitted to Bangour General Hospital with a pulmonary embolus. He required large doses of diuretics to control his pulmonary oedema. Another ventriculogram was performed, showing a further reduction in left ventricular ejection fraction to 8% at a heart rate of 100/minute. It was considered that aneurysectomy would be impossible; cardiac transplant would provide the best prognosis. In May 1988 Mr V.K. had cardiac catheterisation performed, showing total occlusion of the left anterior descending coronary artery. The left ventricular wall was calcified and contracted poorly. Mild pulmonary hypertension was present.

Mr V.K. was on the following medication: Bumetanide 5mg b.d., KCL symp 10ml t.i.d., Captopril 12.5mg b.d., GTN p.r.n., lactulose 10ml nocte and Warfarin 2mg daily.

On examination, Mr V.K. was jaundiced. His pulse was 80/minute and blood pressure was low at 80/50mmHg. J.V.P. was elevated at 15cm and was pulsatile. Gallop rhythm was present but there were no murmurs. The apex beat was palpable in the 6th intercostal space, anterior axillary line, and was sustained throughout systole.

A rocking motion was palpable in systole, moving from medial to lateral across the chest wall towards the apex beat. Peripheral oedema was present to mid thigh level. Examination of the chest revealed bilateral basal crepitations. The abdomen exhibited shifting dullness to percussion and 5cm of smooth hepatomegaly below the costal margin.

Chest X-Ray confirmed gross cardiomegaly and peripheral oedema. An ECG showed freqent ventricular ectopics with Q waves in chest leads V_1- V_6. A diagnosis of severe biventricular failure secondary to ischaemic heart disease was made.

During the week following admission, urea and electrolytes were checked daily. Hyponatraemia on the 6th day (Sodium 131 mmol/l) necessitated cessation of diuretic therapy briefly. Bilirubin was in the range 51 - 68µmol/l during this time. Arrangements with Papworth Hospital in Cambridge were made in preparation for cardiac transplantation.

On 23rd June 1988, eleven days after admission Mr V.K. collapsed in the bathroom. He was cyanosed with fixed dilated pupils. ECG confirmed asystole. Despite all efforts, resuscitation proved unsuccessful. He was declared dead at 9.50a.m. Post mortem examination was not performed.

DISCUSSION

The use of clinical skills in the evaluation of cardiac pathology is becoming less important in this age of high-technology investigations. Yet in the Third World these skills are vital and in Scotland the practitioner should use them to determine which patients require urgent specialist referral.

William Harvey (1628) used his acute but subjective senses to find that "the heart erects itself and raises itself into a point so that at this moment it strikes the chest wall, and externally an impulse can be felt". In the early nineteenth century Laënnec and others held conflicting opinions as to the timing of the apex beat in the cardiac cycle. Espinosa et al (1983) review the early work of Chauveau and Marey from 1855 - 1861. They catheterised the right atrium and both ventricles of anaesthetised horses to measure intracardiac pressure changes and compared this with the onset and duration of the apex beat. They concluded that the cardiac impulse represented the forceful contraction of the heart muscle against the thorax during ventricular systole.

The first authentic case of cardiac aneurysm was reported by Hunter in 1757, although the clinical signs associated with this condition were only elucidated in the early years of the present century. Vakil (1955) looked at 20 cases of proven ventricular aneurysm and found an anomalous location for the cardiac impulse in 50%, a double impulse in 20%, a sustained apex beat in 65% and an undulating or wave-like impulse in 30%. A low pitched systolic murmur extending to early diastole

was also heard in 25% of cases.

In 1963, Deliyannis et al devised an instrument to measure the apical impulse over time, a procedure called apex cardiography. They found that in normal individuals the apical impulse coincided with the first heart sound and had disappeared half way through ventricular systole. They noted that a sustained impulse was characterised by prolongation of the outward impulse up to or beyond the second heart sound. They considered that the sustained impulse could be appreciated on palpation and could be discribed as "heaving" in quality. This sign was found in left ventricular hypertrophy and in patients with ventricular aneurysm. Constrictive pericarditis was associated with an impulse throughout diastole with indrawing of the chest in systole.

Brubakk et al (1982) examined fifteen patients with a sustained apex beat using apex cardiography and other investigations. They found this sign was associated with both dilation and hypertrophy of the left ventricle with various degrees of left ventricular failure clinically.

Other workers used the apex cardiogram to confirm the work of Vakil, finding two chronological thrusts in the apex beat in patients with cardiac aneurysm; traditionally a sign associated with hypertrophic obstructive cardiomyopathy (Nagle et al, 1966). This study on 800 patients by Ahuja and Gutierrez in 1967 also noted a left ventricular rapid filling wave in early diastole in patients with a low left ventricular ejection fraction. They found this to be invariably accompanied by a loud third heart sound at the apex.

Mr V.K., the subject of my case report had a sustained, displaced apex beat with a rolling impulse medial to the cardiac apex. A third heart sound was present and loud. The literature review shows that the sustained apex beat may have been due to his obvious ventricular dilation or caused by his ventricular aneurysm. The rocking impulse medial to the apex has only been described previously in cases of ventricular aneurysm. Mr V.K. had no heart murmurs or double apical impulse which may also be associated with cardiac aneurysm. The third heart sound could be a product of early diastolic ventricular filling as a consequence of very poor left ventricular ejection.

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CASE REPORT 2

Miss E.A. Age 84

Miss E.A. is a spinster living alone in a ground floor Edinburgh flat. She has a sister and niece who visit most days. She herself seldom gets out of the house. A home help comes three times a week. She visits the geriatric day hospital twice weekly by ambulance and has recently had her name added to the sheltered home list. She neither smokes tobacco nor drinks alcohol.

On 4th November 1988 Miss E.A. was admitted to the medical wards in the Royal Infirmary of Edinburgh where I was attached as a student. She could not remember what had happened but the police reported that she had fallen at home and although she telephoned her G.P. she was unable to rise. She had remained on the floor for an hour before the police broke in.

On systemic enquiry, Miss E.A. admitted to dizzyness on looking upwards and occasional palpitations. Recently her appetite had been poor.

Previous medical history included Temporal arteritis 2 years before. Vertigo and dysarthria following a left-sided stroke 5 years previously. She had rheumatic fever as a child. On admission her medication was Digoxin 0.0625mg t.d.s. and Prednisolone 7mg daily.

On examination Miss E.A. was unable to walk but was not distressed. She was dysarthric and dysphonic but with good comprehension of speech. She was mildly tender over the lumbar spine where she fell. Radial pulse was irregularly

irregular, 64/minute. Apex beat was 110/minute, not displaced. Blood pressure was 130/70mmHg. There was no cardiac murmur and no other cardiovascular abnormalities were found, pulses were all present and strong. Respiratory and Abdominal systems were normal. On examination of the Central Nervous System, cranial nerves were intact. Tone was increased bilaterally and power reduced to 4/5 on the left side. Reflexes were as shown below:

	B	Sup	T	K	A	Pl
R:	++	++	+	++	+	↑
L:	++	++	+	+++	+	↓

Sensation was normal but finger-nose co-ordination was poor. Urea and electrolytes were normal. Thyroid function tests were normal. Liver function tests were mildly deranged; Bilirubin 43µmol/l, ALT 36Iu/l and δ-GT 63Iu/l. Random blood glucose was 8.8mmol/l. ECG confirmed atrial fibrillation and showed ST depression and T elevation in the lateral chest leads. At this point the differential diagnosis was Mild stroke, Digoxin toxicity, Vasovagal attack and Myocardial infarction. Prednisolone was increased to 7mg b.d. as the ESR read at 40mm.

On 5th November biochemical tests were repeated. AST was raised at 57Iu/l and urea -stable LDH elevated to 524Iu/l. ECG had not changed from the previous day. The diagnosis now was probable myocardial infarction. On 6th November cardiac enzymes continued to rise.

On 7th November Miss E.A. became pyrexial and incontinent of urine. MSU samples and blood culture failed to grow

organisms. Chest X-Ray was normal, white cell count was 20.5 X 10^9/l. She was slightly confused and paranoid. Augmentin 1.2g was commenced intravenously. AST and LDH had increased to 106Iu/l and 1677Iu/l respectively.

On 8th November, Miss E.A. complained of tiredness. ECG changes of ST depression were resolving. The digoxin level of 1.2nmol/l was thought to be adequate.

On 9th November Miss E.A. developed an intensely painful left leg. Power was reduced to 4/5 and light touch sensation was lost from the left foot. The left popliteal fossa was tender and the left leg was colder and more mottled than the right. Pulses were as shown below:

	Fem	Pop	P.T.	D.P.
R:	++	++	++	+
L:	+	-	-	-

The impression was of an ischaemic left leg with arterial occlusion secondary to cardiac mural thrombus from either myocardial infarction or atrial fibrillation. A vascular surgical opinion was gained and Miss E.A. was transferred to their care for emergency embolectomy.

The surgeon reported that several large thrombi were obtained from the superficial femoral artery, and subsequent foot inspection showed good capillary perfusion and a pink colouration. Cephuroxime 750mg was given pre and post-operatively. 3000 units of Heparin were given post-operatively. Intramuscular Morphine 7.5mg p.r.n. was also prescribed.

On 10th November pulses in the left foot were strong, but the right foot was becoming mottled in colour with absent

pulses. Heparin was stopped and another emergency embolectomy was performed in the same manner as before. On return from theatre pulses in the right foot were strong. Thrombin time ratio was 8:9 so heparin infusion was increased to 1000u/hour. Miss E.A. was confused and aggressive that evening. Droperidol 5mg as well as oral augmentin was prescribed.

On 12th November thrombin time ratio was 19:9. Pulses were all strong with legs exhibiting a good capillary return. Haematological values were normal except for a low haemoglobin of 10.9g/dl. She was transferred back to the medical wards where it was found that the embolectomy scars were healing well. Miss E.A. was still confused, dysarthric and in atrial fibrillation. Haematological and biochemical indices were largely unchanged.

On 15th November Warfarin was commenced. Prednisolone was reduced to 10mg daily with a view to reducing it to 7mg in two days time. ECG showed ST depression had now totally resolved with inverted T waves present in all chest levels. On 17th November heparin was stopped. Miss E.A. continued to mobilise.

On 23rd November the occupational therapists gave Miss E.A. a departmental assessment. Although this and a home visit went well it was considered that Part IV accommodation would be most appropriate for her. Miss E.A. had refused to permit changes to the house lay-out to make it safer. It was thought that at the very least a community care alarm would need to be provided if she was discharged home. Meanwhile she would remain in hospital until problems of accommodation were

resolved. On 16th December 1988 she was still waiting for this.

DISCUSSION

This report on Miss E.A. illustrates a major problem in the management of patients with atrial fibrillation. What is the risk of systemic embolism in atrial fibrillation and under what circumstances should prophylactic measures be taken to discourage embolisation?

Hinton et al (1977) looked at 333 autopsy patients who had atrial fibrillation associated with ischaemic heart disease. He found that systemic emboli could be confirmed in 35% of these patients compared with 7% of a control group without atrial fibrillation. Another study arguing that atrial fibrillation is an independent risk factor for stroke was carried out by Wolf et al in 1978 on the Framingham cohort. He found that out of 5184 men and women followed over 24 years, 481 person-years of atrial fibrillation were observed. He looked at three groups; atrial fibrillation with rheumatic heart disease, idiopathic atrial fibrillation and a control group matched with subjects in the other groups for age, sex and blood pressure. Stroke rate was 2.9/1000 person-years for controls, 41.5/1000 person-years in idiopathic atrial fibrillation and 45.5/1000 person-years in patients with atrial fibrillation and rheumatic heart disease. The difference between the two groups with atrial fibrillation was not significant.

Other factors are important in the genesis of emboli in atrial fibrillation. Petersen and Godtfredsen (1986) looked at the rate of systemic embolism in 426 patients with paroxysmal atrial fibrillation of whom 33.1% developed chronic

atrial fibrillation. It appeared that embolism was much commoner at the onset of paroxysmal atrial fibrillation and also in the first year of chronic atrial fibrillation. Caplan et al (1986) thought that a large left atrium predisposed to embolism in atrial fibrillation. He looked at previous echocardiograms of stroke patients and found that 90% had an enlarged left atrium compared with 10% who had atrial fibrillation without stroke. However Wiener (1987) discovered that in idiopathic atrial fibrillation, neither the size of heart chambers nor underlying heart disease made any difference to rate of embolism.

When should measures be taken to prevent systemic embolism? Some of the earliest work was performed by Cosgriff in 1950. He put 18 patients in atrial fibrillation on Dicumarol after embolism. He reported that 16 of these patients had an uneventful course for 2 years after start of therapy. Many more elegant studies were performed but even in 1986, Starkey and Warlow, reviewing the literature were unable to be certain that a patient with stroke should receive anticoagulants. They believed there had not been an adequate randomised trial performed. The confusion amongst senior physicians in the U.K. on this issue was highlighted by Bucknell et al (1986) who sent questionnaires to 341 consultants. The proportion who would give anticoagulants in the presence of atrial fibrillation ranged from 90% to 27% in different types of mitral disease and to 19% in idiopathic atrial fibrillation. The absence of any consistent policy on therapy is obvious in the figures. Davidson's Principles and

Practice of Medicine (1984) emphasises the importance of treating atrial fibrillation in mitral valve disease with anticoagulants. However work by Roy et al (1986) suggests that the incidence of systemic embolus is reduced by anticoagulants irrespective of underlying pathology or whether fibrillation is paroxysmal or chronic. Sherman et al (1986) showed that the risk of embolus after stroke is about 1% per day in atrial fibrillation. Although anticoagulants reduce this risk, the chance of extending a haemorrhagic cerebral infarct is increased. Roy et al (1986) finds that serious haemorrhagic complications occurred in 2.1/100 patient-years in patients on anticoagulants in his study. Anticoagulants reduced the risk of stroke from 5.5/100 patient-years to 0.7/100 patient-years. Conversion of atrial fibrillation to sinus rhythm should be considered using antiarrhythmic agents or D.C. shock. Digoxin may control the ventricular rate but will not reduce the incidence of embolism. Mancini and Goldberg (1982) report that cardioversion carries the risk of embolism and that this procedure should be covered with anticoagulation for two weeks before and after cardioversion.

Miss E.A., the subject of my case report, was in atrial fibrillation treated with digoxin throughout her stay in hospital. Anticoagulants were started after the first extracerebral embolism but not at a sufficient level to prevent a second. Indeed thrombin time was below the therapeutic level for two days after the second arterial embolism. Although Miss E.A. had rheumatic fever as a child there were no signs of rheumatic heart disease. Possibly her atrial fibrillation

was of "idiopathic" type, the aetiology of which is most probably ischaemic. Miss E.A. had suffered a stroke in the past. It is possible that this was caused by embolism, but this type tends to be a severe stroke with a high mortality. Certainly this lady was fortunate that the emboli lodged in accessible extracerebral arteries. Roy et al (1986) showed that approximately 65% of emboli following atrial fibrillation are in cerebral arteries. Perhaps this lady's mural infarct provided the site for clot formation rather than the fibrillating left atrium. In any case she will need long-term anticoagulation, given that we accept the risk of this therapy in the absence of reliable research to prove its benefit.

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CASE REPORT 3

Mr A.T. Age 40

Mr A.T. is a charge nurse in an Edinburgh Hospital. He recently moved from London with his boyfriend. He describes this homosexual relationship as "solid". He smokes 10 - 15 cigarettes daily and drinks alcohol only occasionally.

He presented to his G.P. with shortness of breath on exertion in October 1988. He was prescribed Erthromycin which seemed to resolve the problem, however, he experienced increasing shortness of breath again with exhaustion even on climbing one flight of stairs. He developed a cough productive of small amounts of white sputum. There was no history of haemoptysis, wheeze or pleuritic pain. With this history he was admitted to the Royal Infirmary on 21st November 1988, six weeks after first consulting his G.P.

Mr A.T. admitted to promiscuous homosexual activities in the early 1980's. In childhood he had an orchidopexy and suffered from Perthes disease of the right hip. He had hepatitis at the age of 30. Since 1986 Mr A.T. has had generalised lymphadenopathy. Oral candidiasis with hairy leukoplakia was diagnosed then at the Middlesex Hospital in London, treated with Nystatin, Ketoconazole and Amphotericin Lozenges. He was generally well until the onset of the present complaint.

On examination Mr A.T. was seen to be communicative but breathless. He was centrally cyanosed and pyrexial, temperature 37.5^{o}c. Oral candidiasis was present. His heart rate

was 110/minute, blood pressure 130/80. He had a grade 2/6 ejection systolic murmur at the cardiac apex. The respiratory system was normal on examination. His abdomen revealed 2cm of smooth hepatomegaly below the costal margin.

A Chest X-Ray was performed which showed extensive consolidation of the right and especially the left lower lobes. Some prominence of both hilar regions was seen. The heart size was normal. Blood tests suggested a low Haemoglobin of 12.6g/dl. Haematocrit of 37.2% was also low. The White cell count was not raised at 8.6 X 10^9/l. Blood chemistry was normal. Arterial blood gas analysis revealed a low pO_2 of 7.4kPa. Blood culture failed to grow organisms. Hepatitis B surface antigen could not be detected.

On the afternoon of 21st November, emergency bronchoscopy was arranged. There was no abnormal anatomy. Lavage was performed with samples sent to laboratories. A few Proteus colonies were grown which were sensitive to cotrimoxazole. Pathology reported several aggregates of Pneumocystitis carinii encysted trophozoites lying in a proteinaceous exudate.

Mr A.T. was counselled about consenting to the test for H.I.V. positivity. He agreed, although on previous occasions had refused to give permission. The result indicated that he had H.I.V. infection. Immune cell monitoring showed severe reduction in CD_4 cells with many activated CD_8 cells, consistent with advanced H.I.V. infection. Monoclonal antibodies to pneumocystis carinii were isolated by the virology laboratory.

A diagnosis of Acquired Immune Deficiency Syndrome was made, complicated by Pneumocystis carinii infection.

Therapeutic measures were instigated: High dose intravenous Cotrimoxazole 2.0g q.i.d., Metoclopramide 10mg t.i.d. orally, Prednisolone 60mg daily and 35% Oxygen were prescribed.

On 22nd November Mr A.T. was more comfortable. He was no longer pyrexial. Fluconazole 50mg daily was prescribed for the oral candidiasis. He complained of reduced hearing on the left. On examination a small red papular lesion was seen in the external auditory meatus. A Kaposi's sarcoma was considered, but an E.N.T. opinion revealed no loss of hearing and no sinister pathology.

On 23rd November the chest was clear on examination. However Chest X-Ray showed no change in the widespread interstitial shadowing. pO_2 and pCo_2 were low at 8.6 and 4.2 kPa respectively. The Clinical Psychologist assessed Mr A.T. and found him to be dismayed at the diagnosis of A.I.D.S. but that it was not totally unexpected to him. He agreed to talk to a previously diagnosed H.I.V. infected volunteer with a view to receiving help from the Edinburgh "buddy" scheme.

On 24th November haematological tests showed that haemoglobin had fallen to 10.7g/dl. White cell and platelet counts were normal. The cytopaenic effects of cotrimoxazole were perhaps being seen in the low haemoglobin level. pO_2 had fallen again to 7.7 kPa.

From 26th to 28th November Mr A.T. was feeling less breathlesss but still without resolution of shadows on X-Ray. pO_2 rose to 8.4 kPa, haemoglobin level was 11.5g/dl.

On 29th November Prednisolone was gradually reduced. Cotrimoxazole was continued. Mr A.T. improved clinically and

was discharged on 2nd December 1988 on Azidothymidine (AZT) 300mg q.i.d. Review was arranged for one week.

DISCUSSION

The emergence of Pneumocystis carinii as a clinically important pathogen and its association with the Acquired Immune Deficiency syndrome has been well documented since 1981. In June of that year the Centre of Disease Control in the United States reported five cases of Pneumocystis carinii pneumonia in homosexual men in the Los Angeles area; the first indication that AIDS was a clinical problem. Previously the protozoa had been described as causing pneumonia largely in malnourished children in Eastern Europe and Iran.

The case report on Mr A.T. illustrates some of the problems in management of Pneumocystis carinii pneumonia.

Firstly there is difficulty in diagnosis. Mr A.T. presented with the typical triad of fever, dyspnoea and hypoxia. Cough is only an occasional feature. X-Ray changes of widespread interstitial shadowing may, together with few clinical signs mimic an acute alveolitis. The history of drug abuse or homosexual activity will however raise the possibility of pneumocystis infection (Stark et al, 1986), but this is not always volunteered.

Problems exist in investigating the illness. Until two years ago, a serological test did not exist for the protozoa. Very seldom do the organisms appear in sputum and lavage will not reveal cysts unless special stains are used, such as methenamine silver (Robbins et al 1984).

Treatment involves the use of antifolate agents to inhibit the dihydrofolate reductaze enzyme in P. carinii. Two agents are currently used; Trimethoprim-sulfamethoxazole

(co-trimoxazole) and Pentamidine isethionate. Sattler et al (1988) compared the two agents. 36 patients randomly received co-trimoxazole, 90 - 120mg/kg/day. They found that co-trimoxazole produced rashes in 44% and anaemia in 39%, with 86% survival at 2 year follow-up. Pentamidine caused nephrotoxicity in 64%, hypotension in 27% and hypoglycaemia in 24%, with 61% survival at 2 year follow-up. The British National Formulary suggests co-trimoxazole as first-line therapy, despite its side-effects, some of which appear to be worse in patients with AIDS. For example tremor has been reported in 4 cases from one centre in Texas sufficient to stop treatment (Borucki et al, 1988). Pentamidine is recommended only when co-trimoxazole has failed to clear the pneumonia and even then only in specialist centres. Nephrotoxicity elevates creatinine levels and occurs commonly. The dose then needs to be adjusted.

If treatment is delayed mortality is high. Superinfection with bacteria, fungi and viruses, especially Cytomegalovirus occurs. Clinical resolution of the pneumonia may only be partial, as reported by el Sadr in 1986; although clinically responsive to co-trimoxazole, trophozoites continued to be present in alveoli of one patient reported.

New drugs are appearing now. Kovacs (1988) showed that Piritrexim would inhibit P. Carinii dihydrofolate reductase at one thousandth the concentration of traditional antifolate drugs in vitro. el Sadr (1986) recommends that drugs capable of destroying trophozoites must be developed if P. carinii is truly to be eradicated in AIDS sufferers.

Mr A.T.'s chest radiograph continued to show signs of infection even at discharge from hospital. In patients like him other drugs to co-trimoxazole may well be necessary, employed in specialist centres to improve the prognosis in this tragic syndrome.

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CASE REPORT 4

Miss M.K. Age 14

Miss M.K. is a Chinese girl attending Boroughmuir School in Edinburgh. She was born in Preston to immigrant parents from Hong Kong. At the age of 1 they moved to Edinburgh where her father works as a chef. She has two sisters aged 19 and 21 and the family live in a small flat on the Royal Mile.

I first met Miss M.K. in the Outpatient department at the Royal Hospital for Sick Children in February 1988. The registrar specialising in diabetes found blood glucose level to be 14mmol/l and expressed surprise that Glycosylated Haemoglobin was 17.6%. He explained that Miss M.K. was both diabetic and thalassaemic but with home circumstances suggesting good motivation for diabetic control.

I thought about the problem, and wondered if the haemoglobinopathy could interfere with measurement of Haemoglobin A_1. I determined to find out about this and more about the patient's medical problems.

At the age of 1, Miss M.K. was diagnosed as having β thalassaemia major during an admission for failure-to-thrive at Edinburgh Royal Hospital for Sick Children. Her sisters and both parents were found to have β thalassaemia minor. Many distant family members in Hong Kong were also known to have thalassaemia. In May 1986 she was admitted with diabetic ketoacidosis and was found to be prepubertal at age 13. Further investigation revealed hypothyroidism. The diabetes mellitus and pan hypopituitarism were considered to be the

result of haemosiderosis, consequent of frequent transfusions for her haemolytic anaemia. Therapeutic measures initiated at this point included Ethinyloestradiol 4ug/day, Thyroxine 150µg/day, Desferrioxamine 2.5g subcutaneously by infusion pump overnight, Insulin given as 30 units Velosulin plus 36 units Insulatard before breakfast and 30 units Velosulin plus 30 units Insulatard before supper.

Haemoglobin concentration was measured fortnightly, and hospital admissions arranged six weekly for infusion of 4 units washed red cells. This tended to raise the haemoglobin from around 9g/dl to 15 or 16g/dl.

When I met Miss M.K. she appeared obese with a height of 1.40m; below the third percentile for her age. Her skin seemed to have a bronze tinge with several fading bruises. She had no pubic hair and only slight breast development. There were no other abnormalities on examination except for a smooth liver edge 1cm below the costal margin. There was no palpable splenomegaly. Investigations showed normal urea and electrolyte levels. Serum ferritin was grossly raised at 4115µg/ml. Serum iron was moderately raised at 65µmol/l.

Miss M.K. began to experience hypoglycaemic attacks in June 1987. In September of that year her notes included the comment that Glycosylated haemoglobin was consistently and unacceptably high, especially since haemolytic anaemia is usually associated with a low Haemoglobin A_1 due to a high red cell turnover. As a result her evening insulin was increased to 32 units Velosulin plus 32 units Insulatard. She continued to experience hypoglycaemic episodes.

Miss M.K. is a well motivated patient with a supportive family. Her good command of English helps in education about her medical problems but the future surely holds many difficulties for this girl. Medical problems must be treated aggressively and lifestyle will thus be radically affected if she is not to have a very guarded prognosis.

DISCUSSION

Shortly after seeing Miss M.K. in the Diabetic Out-Patient clinic I reviewed the literature to discover any record of abnormal haemoglobin molecules interfering with measurements of glycosylated haemoglobin levels. I found a number of relevant references.

The routine methods for measuring glycosylated haemoglobin (Haemoglobin A_1) in diabetes are agar gel electrophoresis and column chromatography. These depend on glycosylated haemoglobin having a different electrical charge to adult haemoglobin. The tests do not distinguish between glycosylated haemoglobin and foetal haemoglobin which both migrate together (Paisley et al 1984 a).

Hall et al (1983) showed that the use of simple affinity chromatography to measure haemoglobin A_1 gave a falsely high value if foetal haemoglobin was present in the blood. Paisley et al (1984 a) reported two cases of insulin-dependent diabetic women with persistently high glycosylated haemoglobin levels as measured by agar gel electrophoresis. This was associated with only moderately raised blood glucose; an unexpected finding. Both patients had recently been prescribed greater amounts of insulin on the basis of haemoglobin A_1 levels, and both experienced frequent hypoglycaemic episodes as a result. Foetal haemoglobin was measured and was found to be present in their blood at 2.6% and 5.0% (normal levels <0.7%). When Haemoglobin A_1 was measured in these patients using a thiobarbituric acid reaction, a lower value was found; more consistent with the blood glucose readings. These workers

recommended that agar gel electrophoresis should not be used in pregnant diabetic women or in haemoglobinopathies, which may be associated with high levels of foetal haemoglobin. Saitta et al (1984) studied 32 non-diabetic mothers of babies with thalassaemia and found that glycosylated haemoglobin levels using a chromatographic method were higher than in controls (9.3% compared with 7.1%). This difference was especially marked in mothers who had detectable levels of foetal haemoglobin.

These studies illustrate the problem of using electrophoretic or chromatographic methods in the measurement of glycosylated haemoglobin when foetal haemoglobin is also present in the blood. Paisley et al (1984 a) suggest that a thiobarbituric acid reaction would give more accurate results. In a separate report they find glycosylation of human hair also to be a useful indicator of diabetic control (Paisley et al, 1984 b). Hall et al (1983) suggest that measurement of glycosylated plasma proteins might be valuable too in determining medium-term diabetic control in the presence of foetal haemoglobin.

β-thalassaemia is a haemoglobinopathy characterised by lack of β globulin chain synthesis of adult haemoglobin. Foetal haemoglobin consisting of two alpha chains and two gamma chains ($\alpha_2 \gamma_2$) is present, together with haemoglobin A_2 ($\alpha_2 \delta_2$) and sometimes normal adult haemoglobin ($\alpha_2 \beta_2$). Miss M.K. did not have foetal haemoglobin measured, but after attention was drawn to the above studies, glycosylated haemoglobin levels were no longer used to determine her

diabetic control. Her evening insulin requirements were also reduced from 32 to 30 units of Velosulin and Insulatard.

An additional problem of thalassaemic patients is reported by Kattamis et al (1987). They found a marked increase in renal glucose threshold in these patients compared to controls. Thus in thalassaemia, glycosuria may also be misleading in the assessment of diabetic control.

References

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